Epitomes

Important Advances in Clinical Medicine

Obstetrics and Gynecology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in obstetrics and gynecology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association, and the summaries were prepared under its direction.

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Diabetes Mellitus in Pregnancy

DIABETES MELLITUS or glucose intolerance in pregnancy carries substantial risk to both mother and fetus. Maternal risks include increased rates of pregnancy-induced hypertension, cesarean section with attendant morbidity, and polyhydramnios and spontaneous abortion. Fetal risks include developmental anomalies, birth trauma, and intrauterine asphyxia and death. The newborns of diabetic women are subject to hypoglycemia, hyperbilirubinemia, and electrolyte disturbances, especially of calcium levels. Female newborns are at an increased risk of having glucose intolerance in future pregnancies.

Whereas the diagnosis is obvious in women who are already insulin-dependent, carbohydrate intolerance would be undetected without the appropriate screening evaluation in the majority of at-risk pregnant women. By definition, gestational diabetes is carbohydrate intolerance of variable severity, first occurring or first being recognized during pregnancy. All pregnant women should have a plasma glucose determination an hour after consuming 50 grams of glucose as a flavored solution. Testing is usually done at 28 weeks of gestation. Pregnant women with "high-risk" factors such as previous stillbirth, a previous infant with a congenital anomaly, or a previous macrosomatic infant (greater than 4,500 grams) should be tested at the first prenatal visit. If testing results are normal, the test should be repeated at 28 weeks of gestation. Values greater than 7.8 mmol per liter (140 mg per dl) require a formal three-hour glucose tolerance test. After fasting and baseline sampling, 100 grams of glucose is taken. Normal plasma glucose values are as follows: fasting, less than 5.7 mmol per liter (105 mg per dl); after one hour, less than 10.5 mmol per liter (190 mg per dl); after two hours, less than 9.2 mmol per liter (165 mg per dl); and after three hours, less than 8.0 mmol per liter (145 mg per dl). Two abnormal values constitute carbohydrate intolerance and a diagnosis of gestational diabetes.

Maternal morbidity is greatly reduced in women with gestational diabetes when a comprehensive management plan is developed by the primary care physician in consultation with a perinatologist. The plan should begin with diet counseling, education, and glucose monitoring. Insulin therapy is indicated when fasting and postprandial glucose determinations are persistently greater than 5.7 and 6.7 mmol per liter (105 and 120 mg per dl), respectively.

Perinatal morbidity and mortality are reduced through close fetal surveillance in the third trimester in pregnant women who are insulin-dependent. Testing for fetal well-being should be started at 32 weeks of gestation. The fetal nonstress test, in combination with amniotic fluid volume assessment, should be done two to three times a week. The nonstress test evaluates the fetal heart rate response to fetal movement during a 20-minute recording of the fetal heart rate. Accelerations of the fetal heart rate with fetal movement suggest no compromise of fetal well-being. The absence of accelerations of the fetal heart rate or decelerations suggest fetal compromise and require further testing. The fetus may be "stressed" by inducing uterine contractions and the heart rate response evaluated. If no fetal heart rate decelerations occur with three contractions spaced two to three minutes apart, fetal well-being is established. Amniotic fluid volume is determined with the use of ultrasonography. Fluid pockets are measured in each of the four quadrants of the amniotic cavity and then totaled as the "amniotic fluid index." An index greater than 5 cm is considered normal. As an alternative to stressing the fetus, when the nonstress test results are abnormal, an ultrasound evaluation for fetal breathing movement, fetal tone, and fetal movement may be used. Two of these three variables as seen on ultrasonogram, along with a normal amniotic fluid index, are consistent with good fetal status. Estimates of fetal weight by ultrasonogram at three-week intervals enhance the ability to diagnose fetal macrosomatia.

There is no uniform agreement in the approach to fetal surveillance in pregnant women whose diabetes is well controlled with diet. Data suggest that these women and their fetuses may benefit from weekly fetal surveillance. Two thirds of the members of the Society of Perinatal Obstetricians use some form of fetal surveillance in uncomplicated gestational diabetes. More frequent testing is indicated in diet-controlled patients in whom pregnancy-induced hypertension or the need for insulin therapy develops or who have a history of stillbirth.

Delivery is indicated when the maternal or fetal condition deteriorates. These situations include the development of

pregnancy-induced hypertension or a history of decreased fetal movement supported by persistently poor fetal testing over one to two days. Pregnancy should rarely be carried beyond 40 weeks except in women well controlled by diet with no other risk factors. In such situations, fetal surveillance should be used until cervical ripening or 42 weeks of gestation. Elective interventions, such as a cesarean section at 38 weeks or inductions of labor, should be preceded by evidence of fetal lung maturity.

The long-term morbidity of gestational diabetes includes type II or non–insulin-dependent diabetes mellitus. This disorder in turn is associated with a higher frequency of end-organ failure, such as kidneys, eyes, and heart, especially in minority populations. Continued attention to diet, weight control, and exercise may reduce these risks.

At eight weeks postpartum, women with gestational diabetes mellitus should be tested with a standard 75-gram, two-hour glucose tolerance test. Women with abnormal test results should be seen by a diabetologist.

Although the risk of congenital anomalies is not reduced by diagnosing diabetes during pregnancy, this approach identifies a population that should undergo preconception counseling. Such counseling begins before the next pregnancy, which should be planned. It encourages women at risk for gestational diabetes to begin good glucose control two to three cycles before a planned pregnancy. This approach is associated with a substantial reduction in congenital anomalies.

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RU 486 (Mifepristone)

RECENTLY APPROVED for use as an abortifacient in the United Kingdom and in France, RU 486 (mifepristone) is the first of a new class of antiprogestins. When given in early pregnancy, it saturates progesterone receptors in the endometrium but does not act as an agonist. Progesterone is essential to sustain an early pregnancy, and if its action is blocked by RU 486, an abortion ensues. When given in a single oral dose of 600 mg before seven weeks' gestation, abortion rates of 80% to 90% can be achieved. If the dose of RU 486 is followed in 36 to 48 hours by a small dose of prostaglandin, the efficacy increases to more than 90%. The prostaglandin can be given as an intramuscular injection, a vaginal suppository, or orally by tablet. In the largest series of such abortions reported from France, the abortion rate was 96%. Morbidity rates have been low, although heavy bleeding can require curettage for management.

RU 486 may have a broad range of uses in reproductive medicine. When given to both pregnant and nonpregnant women, it causes softening and dilation of the cervix. When given 24 hours before beginning a second-trimester abortion by labor induction, it can reduce the time required by more than 50%. Its usefulness for inducing labor at term remains to be studied. Experience with RU 486 as medical therapy for ectopic pregnancy has not been encouraging. One small study found that daily treatment of endometriosis with RU 486 for three months led to a relief of symptoms without objective lessening in the extent of disease.

RU 486 may have applications beyond reproductive medicine. For example, the drug might be useful in treating women with metastatic breast cancer resistant to current therapies. In a study of 22 women after menopause or oophorectomy with therapy-resistant metastatic breast cancer, 18% showed a response to the drug at three months. When given in doses larger than that required to block progesterone receptors, RU 486 also blocks glucocorticoid receptors; the drug has been shown to be useful in treating Cushing's syndrome. Studies of its use in treating glaucoma and meningioma are in progress.

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Management of Hirsutism

HIRSUTISM, or male-pattern hair growth in women, is a common cosmetic complaint. The differential diagnosis includes pathophysiologic processes that either increase androgen production (polycystic ovary syndrome, late-onset congenital adrenal hyperplasia, Cushing's syndrome, or neoplasm) or increase androgen activity at the hair follicle itself (increased 5α-reductase activity). Regardless of the cause, the presence of hirsutism implies a net hyperandrogenic effect at the hair follicle. Evaluation requires a careful physical examination and the measurement of serum androgens (testosterone and dehydroepiandrosterone). The physical examination should include areas of male-pattern hair growth such as the upper lip, chin, neck, midline chest, and lower abdomen. If serum androgen levels are elevated—testosterone greater than 1.8 nmol per liter, dehydroepiandrosterone greater than 9.5 μmol per liter—then disorders of androgen overproduction such as polycystic ovary syndrome or late-onset congenital adrenal hyperplasia should be considered. If serum androgen levels are normal, then increased 5α-reductase activity is diagnosed by exclusion. Once a diagnosis has been made, treatment can be considered. The cornerstones of medical treatment involve inhibiting adrenal or ovarian androgen production; altering androgen binding to sex hormone-binding globulin (SHBG); or blocking androgen receptors.

Ovarian androgen production can be suppressed in several ways. The use of combination estrogen-progestin (oral contraceptive) therapy lowers free testosterone levels by suppressing ovarian production of androgens and increasing SHBG. Because hirsutism is commonly associated with menstrual irregularities, oral contraceptives can also provide menstrual cycle control. Gonadotropin-releasing hormone agonists, such as leuprolide acetate or nafarelin acetate, have been used successfully to treat hirsutism by inhibiting ovarian androgen production. Because of the effects of estrogen deprivation, however, long-term treatment with these agents is not feasible.

Selective suppression of adrenal androgen production may be induced with low dosages of dexamethasone. This is